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PATENT ABSTRACTS OF JAPAN

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(71)Applicant : HISAMITSU PHARMACEUT CO INC
(72)Inventor : NAKAGAWA AKIRA
HIRANO MUNEHIKO
TAKADA YASUNORI

(54) ANTIPHLOGISTIC ANALGESTIC PLASTER

(57)Abstract:
PURPOSE: To provide an anti-phlogistic analgestic plaster having excellent drug ingredient releasability, skin permeation amount, skin permeation degree and persistent and constant volume drug ingredient releasability even when attached for a long period.
CONSTITUTION: A plaster contains styrene-isoprene-styrene block copolymer, crotamiton and an anti-phlogistic analgestic drug ingredient as essential ingredients. Slightly soluble 4-biphenylacetic acid is most preferable among the antiphlogistic analgestic drugs, and a combination thereof with the styrene- isoprene-styrene block copolymer and the crotamiton gives the most preferable anti-phlogistic analgestic plaster.

LEGAL STATUS

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WHAT IS CLAIMED IS:

1. Antiphlogistic analgestic plaster which is essentially based on styrene - isoprene - styren block copolymer, crotamiton and anti - phlogistic analgesic drug.

2. Antiphlogistic analgestic plaster which are essentially based on styrene - isoprene - styren block copolymer 5-50 % by weight, crotamiton 1-20 % by weight and anti - phlogistic analgesic drug 0,1-10 % by weight.

3. Antiphlogistic analgestic plaster of Claim 1 and Claim 2 is characterized by that anti - phlogistic analgesic is 4 - biphenylacetic acid or 4 - biphenylacetic acid ethyl ester.

DETAILED DESCRIPTION OF THE INVENTION

[0001]

INDUSTRIAL APPLICATION FIELD

This investigation relates to the antiphlogistic analgetic plaster which is essentially based on styrene - isoprene - styren block copolymer, crotamiton and anti - phlogistic analgesic.

[0002]

PRIOR ART

In patch containing anti - phlogistic analgesic, the example which combination prescribed natural rubber, polymer of polyacrylic acid system, synthesis polyisoprene rubber, polystyrene polybutadiene rubber, polyisobutylene, silicone rubber, lipophilic polymer of styrene - isoprene - styren block copolymer, terpene resin, petroleum resin, tackifier of ester gum, process oil, Polybutene, liquid paraffin, castor oil, cotton seed oil, palm oil, coconut oil, tenderizer of lanolin, zinc oxide, titanium dioxide, each base of filler of silica-base for as base appropriately is being known about in a person skilled in the art broadly.

In addition, 4 - biphenylacetic acid and 4 - biphenylacetic acid ethyl ester are already marketed as gel ointment (a Japanese Patent Laid-Open No. 59 - 222409 bulletin) or injection of fat emulsion (a Japanese Patent

Laid-Open No. 61-44809 bulletin) in antiinflammatory analgesic.

[0003]

PROBLEM TO BE SOLVED BY THE INVENTION

It is not enough, there is a problem in point of availability of biology in development of crystal deposition, percutaneous absorption nature, drug efficacy expression nature, the drug efficacy durability solubility for base or solvent anti - phlogistic analgesic of drug efficacy constituent as resolution analgestic plaster by the publicly known which described as above or well-known plaster prescription badly.

In addition, most of the 4 - biphenylacetic acid of poor solubility or the pasting pharmaceutical on the ethyl ester compound is not examined in anti - phlogistic analgesic, besides, there was a problem as injection method of assay only with gel ointment or injection.

[0004]

MEANS TO SOLVE THE PROBLEM

As a result of the present invention should have solved previously described problems, and having studied it zealously, what can be solved by what is done with styrene - isoprene - styren block copolymer, crotamiton and the combination prescription which are essentially based on anti - phlogistic analgesic is found, it made the present invention complete.

In anti - phlogistic analgesic in particular, because 4 - biphenylacetic acid (a generic name: felbinac) is insoluble or poor soluble in various menstruum such as alcohol, water, glycol, isopropyl myristate, even if it is combined with each base, the 4 - biphenylacetic acid which is anti - phlogistic analgesic does not dissolve enough it, and is taken in in base in form of crystal, absorption as opposed to skin and drug efficacy expression nature was not desirable.

Thus as a result of having studied it zealously, crotamiton extremely found a superior thing in decomposition ability unexpectedly.

In addition, crotamiton and combination with various lipophilic polymers were examined in various ways, combination with styrene - isoprene - styren block copolymer found the most preferred thing.

In addition, it was found that 4 - biphenylacetic acid ethyl ester (a generic name: felbinac ethyl) was combined, and a similarly preferred result

was got.

[0005]

Combination prescription of each base of the present invention was examined more in detail, it was found the thing that most preferably was done with combination prescription comprising of styrene - isoprene - styren block copolymer 5-50 % by weight, more preferably 10-30 % by weight, crotamiton 1-20 % by weight, that more preferably it appeared by 2-10 % by weight, anti - phlogistic analgesic 0.1-10 % by weight, more preferably 0.5-5 % by weight .

[0006]

In addition, anti - phlogistic analgesic is meant as clinical done drug which is already marketed or investigational new drug, for example, indometacin, ketoprofen, flurbiprofen, loxoprofen sodium, diclofenac sodium, piroxicam, meloxicam, bermoprofen, lornoxicam, ketorolac, morphine, buprenorphine, butorphanol, pentazocine, fentanyl, eptazocine are given.

[0007]

It is contained optimum dose combination of inorganic filler such as zinc oxide, aluminium oxide, titanium dioxide, silica, magnesium oxide, iron oxide, zinc stearate; tackifier rosin system resin such as [Ester gum (Arakawa Chemistry), HARIESTER (Satsuma Kasei), HARITACK (Satsuma Kasei)], terpenoid resin [Y S resin (Yasuhara Fat), Pico light (Hercurie)], petroleum system resin [ARKON (Arakawa Chemistry), レガレッシ (Hercurie), ESCOREZ(Exxon), wing tackiness (Goodyear)], phenolic system resin, xylene resin; tenderizer such as liquid paraffin, castor oil, cotton seed oil, palm oil, coconut oil, lanolin; oxidation inhibitor of publicly known such as dibutyl hydroxytoluene, for example, in addition to the required ingredient appropriately conventionally by patch of the present invention.

[0008]

In addition, as support of the present invention, the thing which does not influence ejection of a drug is desirable, and, the expansion and contraction nature and a thing of the non-expansion and contraction nature are used.

For example, it is chosen from film or sheet or lamination body of polyethylene, polypropylene, polybutadiene, ethylene vinyl acetate

copolymer, polyvinylchloride, polyester, nylon, polyurethane, as a synthetic resin membrane porous body, foam, paper, cloth and nonwoven fabric.

[0009]

A description is made of a manufacturing process of resolution antiphlogistic analgestic plaster of the present invention.

At first styrene - isoprene - styren block copolymer, tenderizer, tackifier and filler are added in appointed rate appropriately, it is with mixture, and it is done, heat is agitated between nitrogen gas stream, and it is done with dissolution thing.

Temperature in agitation is 110-200 degrees Celsius, and agitation time is 30-120 minutes.

[0010]

A drug efficacy ingredient and a mixture of crotamiton are doped in field of temperature 110 - 200 degrees Celsius in agitation of the decomposition thing next, it is mixed for 5-30 minutes, and the dissolution thing which is uniformity is got.

This decomposition thing is spread and applied in support by means of spreader such as doctor roll, a reverse roll next.

It is chosen among a synthetic resin membrane, paper, cloth, a nonwoven fabric in support, and it is used.

After having spread decomposition thing on support, thereupon, abrasion coating is patched together, which can be chosen among film such as polyethylene, polypropylene, polyester, exfoliation paper which spent abrasion disposal, or cellophane appropriately.

Plaster of the present invention is provided by a described manufacturing process as things mentioned above.

[0011]

EXAMPLE

Examples, Test examples are given as follows, and the present invention is explained more in detail.

In addition, in Examples, Comparative examples, Reference examples, part mean all part by weight.

[0012]

Example 1

Styrene - isoprene - styren block copolymer 50.0 parts (trade name calif lek TR -1107)

Liquid paraffin 46.9 parts

Bytyl hydroxy toluene 2.0 parts

Crotamiton 1.0 parts

4 - biphenylacetic acid 0.1 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0013]

Example 2

Styrene - isoprene - styren block copolymer 5.0 parts (trade name calif lek TR -1107)

Liquid paraffin 35.0 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (alicycle group saturated hydrocarbons resin) 28.0 parts (trade name ARKON P -100)

Crotamiton 20.0 parts

4 - biphenylacetic acid 10.0 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0014]

Example 3

Styrene - isoprene - styren block copolymer 26.0 parts (trade name calif lek TR -1107)

Liquid paraffin 42.0 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE-311)

Crotamiton 10.0 parts

4 - biphenylacetic acid 5.0 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0015]

Example 4

Styrene - isoprene - styren block copolymer 12.5 parts (trade name calif

lek TR -1107)

Styrene - isoprene - styren block copolymer 12.5 parts (trade name calif lek TR -1111)

Liquid paraffin 51.0 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE -311)

Crotamiton 5.0 parts

4 - biphenylacetic acid 2.0 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0016]

Example 5

Styrene - isoprene - styren block copolymer 25.0 parts (trade name calif lek TR -1111)

Liquid paraffin 52.0 parts

Bytyl hydroxy toluene 2.0 parts

Crotamiton 15.0 parts

Tackifier (rosin ester) 5.0 parts (trade name KE - 311)

4 - biphenylacetic acid 1.0 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0017]

Example 6

Styrene - isoprene - styren block copolymer 21.0 parts (trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 53.5 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE -311)

Crotamiton 2.5 parts

4 - biphenylacetic acid 1.0 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0018]

Example 7

Styrene - isoprene - styren block copolymer 20.0 parts (trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 52.0 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE-311)

Crotamiton 5.0 parts

4 - biphenylacetic acid 1.0 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0019]

Example 8

Styrene - isoprene - styren block copolymer 18.0 parts (trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 49.0 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) (trade name KE -311) 15.0 parts

Crotamiton 10.0 parts

4 - biphenylacetic acid 1.0 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0020]

Example 9

Styrene - isoprene - styren block copolymer 20.0 parts (trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 52.0 parts

Bytyl hydroxy toluene 15.0 parts

Tackifier (rosin ester) 2.0 parts (trade name KE-311)

Crotamiton 5.0 parts

4 - biphenylacetic acid ethyl 1.0 parts

It is made in accordance with the manufacturing process in this

prescription, it was cut in desired size, and it was done with plaster.

[0021]

Example 1 0

Styrene - isoprene - styren block copolymer 20.0 parts (trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 50.0 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE -311)

Crotamiton 6.0 parts

Indometacin 2.0 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0022]

Example 1 1

Styrene - isoprene - styren block copolymer 19.0 parts (trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 49.0 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE -311)

Crotamiton 7.0 parts

Ketoprofen 3.0 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0028]

Example 1 2

Styrene - isoprene - styren block copolymer 20.0 parts (trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 52.0 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE -311)

Crotamiton 5.0 parts

Flurbiprofen 1.0 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0029]

Example 1 3

Styrene - isoprene - styren block copolymer 19.0 parts of (trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 49.0 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE -311)

Crotamiton 7.0 parts

Loxoprofen sodium 3.0 parts

It is made in accordance with the manufacturing method in this prescription, it was cut in desired size, and it was done with plaster.

[0030]

Example 1 4

Styrene - isoprene - styren block copolymer 20.0 parts (trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 52.0 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE-311)

Crotamiton 5.0 parts

Diclofenac sodium 1.0 parts

It is made in accordance with the manufacturing method in this prescription, it was cut in desired size, and it was done with plaster.

[0031]

Example 1 5

Styrene - isoprene - styren block copolymer 20.0 parts (trade name calif lek TR -1111)

Polyisobutylene (made by exxon chemistry) 5.0 parts

Liquid paraffin 50.0 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE -311)

Crotamiton 6.0 parts

Piroxicam 2.0 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0032]

Example 1 6

Styrene - isoprene - styren block copolymer 21.0 parts(trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 53.5 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester)15.0 parts (trade name KE -311)

Crotamiton 3.0 parts

Meloxicam 0.5 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0033]

Example 1 7

Styrene - isoprene - styren block copolymer 21.0 parts (trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 53.5 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester)15.0 parts (trade name KE -311)

Crotamiton 3.0 parts

Bermoprofen 0.5 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0034]

Example 1 8

Styrene - isoprene - styren block copolymer 21.0 parts (trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 53.5 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE-311)

Crotamiton 3.0 parts

Lornoxicam 0.5 parts

It is made in accordance with the manufacturing process, in this prescription, it was cut in desired size, and it was done with plaster.

[0035]

Example 1 9

Styrene - isoprene - styren block copolymer 21.0 parts (trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 53.5 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE -311)

Crotamiton 3.0 parts

Ketrolac 0.5 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0036]

Example 2 0

Styrene - isoprene - styren block copolymer 23.0 parts (trade name calif lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 53.9 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE -311)

Crotamiton 1.0 parts

Fentanyl 0.1 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0037]

Example 2 1

Styrene - isoprene - styren block copolymer 23.0 parts (trade name calif

lek TR -1111)

Polyisobutylene (made by exon chemistry) 5.0 parts

Liquid paraffin 53.9 parts

Bytyl hydroxy toluene 2.0 parts

Tackifier (rosin ester) 15.0 parts (trade name KE -311)

Crotamiton 1.0 parts

Eptazocine 0.1 parts

It is made in accordance with the manufacturing process in this prescription, it was cut in desired size, and it was done with plaster.

[0038]

Comparative example 1

The patch was got to with a similar method Example 7 except crotamiton .

[0039]

Test example 1 (a drug release examination)

Discharge of drugs from plasters provided in Example 6, 7, 8, Comparative example 1 to the water is examined, drug release factor from the whole plasters was demanded.

The result is shown in table 1.

[0040]

[table 1]

Drug release rate after four hours (%)

Example 6 38.18 ± 2.12

Example 7 46.28 ± 3.36

Example 8 48.23 ± 2.88

Comparative example 1 22.85 ± 1.05

[0041]

Test example 2 (a hairless laboratory mouse skin penetration examination)

The plaster of Example 7 and the ointment which contains 4 - biphenylacetic acid of existing release (trade name: NAPAGELN ointment) as a comparison medicine are used for a hairless laboratory mouse skin penetration examination. Skin penetration quantity and availability (skin penetration rate) of 4 - biphenylacetic acid after eight hours were demanded.

The result is shown in table 2.

[0042]

[table 2]

Quantity of skin penetration (μ g)

Example 7 13.68 ± 0.87

NAPAGELN ointment 7.45 (trade name) ± 1.69

Quantity of drug administration (μ g)

Example 7 116.82

NAPAGELN ointment 235.99

Availability (%)

Example 7 11.7 ± 0.7

NAPAGELN Ointment 3.05 ± 0.7

[0043]

OPERATION

In a drug release examination of Test example 1, the plaster which is essentially based on styrene - isoprene - styren block copolymer crotamiton and anti - phlogistic analgesic of the present invention, shows about 2 times drug release factor in reference with plaster of the Comparative examples that does not contain crotamiton.

In addition, in a hairless laboratory mouse skin penetration examination of Test example 2, the plaster of the present invention shows about 2 times quantity of skin penetration and about 4 times availability (skin penetration rate) in reference with the commercial drug (trade name: NAPAGELN ointment) as a comparison medicine.

In addition, the plaster of the present invention had very preferred action in a respect of physical property (adhesive force, anchoring power, cohesion, stickiness).

[0044]

EFFECT OF THE INVENTION

Having the function which is significant in drug release nature, a quantity of skin penetration and skin permeability plaster of the present invention, it is collected, high drug efficacy expression nature is possible.

In addition, there is a little use quantity of the anti - phlogistic

analgesic which is a drug efficacy ingredient, and it is finished and is economical.

In addition, it is different from gel ointment or injection, and drug release is possible stably, and even pasting is superior in the durability in pharmaceutical of the present invention being plaster for a long time.

As thus described plaster of the present invention is very useful for drug release in the most suitable pharmaceutical or pharmaceutical industry.